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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,744	04/24/2001	Jorge F. DiMartino	12636-891	5759

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	8

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,744	DIMARTINO, JORGE F.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-14 and 16-38* is/are pending in the application.

4a) Of the above claim(s) *3,29 and 31-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-14,16-28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1, 3-14 and 16-38 are pending.

Applicants' amendment filed on September 17, 2002 (Paper No. 7) is acknowledged, and applicants' response has been fully considered. Claims 1, 4, 5, 31 and 36 have been amended, and claims 2, 15 and 39-43 have been cancelled. Claims 3, 29 and 31-38 are non-elected inventions and are withdrawn from consideration. Thus, claims 1, 4-14, 16-28 and 30 are examined.

Objection Withdrawn

2. The previous objection of claim 4, is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 3 in Paper No. 7.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1, 2, 4, 6-9, 13-18, 27, 28, 30, 39 and 40, under 35 U.S.C. §112, first paragraph, is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim, and applicants' response at pages 4-5 in Paper No. 7.

4. The previous rejection of claims 1, 2, 4, 6-9, 13-18, 27, 28, 30, 39 and 40, under 35 U.S.C. §112, second paragraph, regarding the term "a disease associated with aberrant silencing of gene expression", "cytidine analog", "FR901228", "MS-27-275" or "one or more", is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim, and applicants' response at pages 6-7 in Paper No. 7.

Claim Rejections - 35 USC § 102&103

5. The previous rejection of claims 1, 2, 4, 6-8 and 12 under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Guan *et al.* (Cancer Research 60, 749-755 (February 2000)) is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim, and applicants' response at pages 7-8 in Paper No. 7.

Claim Rejections - 35 USC § 103

6. The previous rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Guan *et al.* (Cancer Research 60, 749-755 (February 2000)) in view of Cameron *et al.* (Nature Genetics 21, 103-107 (January 1999)), is withdrawn in view of applicants' amendment to the claim, and applicants' response at pages 8-9 in Paper No. 7.

7. The previous rejection of claims 28 and 30 under 35 U.S.C. 103(a) as being unpatentable over Guan *et al.* in view of Boyd *et al.* (U. S. Patent 5,283,383), is withdrawn in view of applicants' amendment to the claim, and applicants' response at page 9 in Paper No. 7.

Claim Objections

8. Claims 4 and 28 are objected to because the claim contains non-elected inventions, e.g., claim 4 contains gallstone, which is not cancer, and claim 28 contains non-elected anti-neoplastic agents such as alkylating agents.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1, 4-14, 16-28 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-14, 16-28 and 30 are indefinite because the claim lacks essential steps in the method of treating cancer with a combination therapy. The omitted step is the outcome of the treatment. Claims 4-14, 16-28 and 30 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

In response, applicant indicates the step of administration and the doses of the two agents have been cited in the claim. The argument is not fully persuasive because the end point of the treatment which is essential in the method of treatment is not cited.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 4-10, 13, 14, 16-18, 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubinfeld *et al.* (US 2002/0114809 A1, filed February 21, 2001) in view of Yang *et al.* (Cancer Research 60, 6890-6894 (December 2000)).

Rubinfeld *et al.* teach a method of treating a patient with cancer comprising administering a therapeutically effective amount (e.g., 2-50 mg/m^2 per day, paragraph 0114) of a DNA methylation inhibitor such as decitabine (claims 6 and 7) in combination with an effective amount of an antineoplastic agent such as an antibiotic agent (paragraphs 0007, 0008 and 0077;

claims 28 and 30). Various types of cancers including breast cancer, skin cancer and other cancers are being treated (paragraph 0019; claims 4 and 5). The DNA methylation inhibitor decitabine is administered to a patient via a 1-24 hour i.v. infusion per day for 3-5 days per treatment cycle at a dose ranging from 1-1000 mg/m^2, preferably 1-200 mg/m^2, more preferably 2-50 mg/m^2, and most preferably 5-20 mg/m^2 (paragraph 0114, claims 13, 14, 16-18). However, Rubinfeld *et al.* do not disclose the use of a histone deacetylase (HDA) inhibitor for the treatment of cancer. Zhu *et al.* teach HDA inhibitors, depsipeptide (FR901228) and trichostatin A induce apoptotic cell death, and this induced apoptosis is greatly enhanced in the presence of the DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (pages 1328-1331; claims 8-10). At the time of invention was made, it would have been obvious to one of ordinary skill in the art to treat cancer using the agent taught by Rubinfeld *et al.* in combination with a HDA inhibitor as indicated by Zhu *et al.* (claim 1) because the DNA methyltransferase inhibitor can enhance the apoptosis induced by the HDA inhibitor, thus the combination therapy would produce the synergic effect of the two agents. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

11. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rubinfeld *et al.* in view of Yang *et al.* as applied to claims 1 and 8 above, further in view of Saito *et al.* (Proc. Natl. Acad. Sci. U.S.A. 96, 4592-4597 (1999)).

Rubinfeld *et al.* teach a method of treating a patient with cancer comprising administering a therapeutically effective amount (e.g., 2-50 mg/m^2 per day, paragraph 0114) of a DNA methylation inhibitor such as decitabine in combination with an antineoplastic agent such as an antibiotic agent (paragraphs 0007, 0008 and 0077). Zhu *et al.* teach HDA inhibitors,

depsipeptide (FR901228) and trichostatin A induce apoptotic cell death, and this induced apoptosis is greatly enhanced in the presence of the DNA methyltransferase inhibitor, 5-aza-2'-deoxycytidine (pages 1328-1331; claim 8). The combined references teach the treatment of cancer with a combination therapy of decitabine and trichostatin A (claim 1). However, Rubinfeld *et al.* and Zhu *et al.* do not disclose the use of MS-27-275 or butyrate as the HDA inhibitor. Saito *et al.* disclose the benzamide derivative MS-27-275 has marked in vivo antitumor activity through HDA inhibition (pages 4594-4595), and also indicate another HDA inhibitor sodium butyrate has been known to arrest the cell cycle and provide various differentiation phenotypes or revertant phenotypes to cancer cells (page 4592). Therefore, at the time the invention was made, it would have been obvious to a person of ordinary skill in the art to treat cancer with a combination therapy of a DNA methylation inhibitor and a HDA inhibitor as taught by Rubinfeld *et al.* and Zhu *et al.* and substituting with a different HDA inhibitor such as MS-27-275 or butyrate as indicated by Saito *et al.* for treating cancer because the use of decitabine and MS-27-275 or butyrate would provide an alternative combination therapy for treating various cancers. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

12. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
Patent Examiner

June 8, 2002

Christopher S. F. Low

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